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A Review on Biochemical Aspects of Schizophrenia

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ABSTRACT

Schizophrenia is a severe disorder affecting the brain. Defective neurotransmitters and altered neurotransmission system maybe one of the various causes for this psychiatric disease. There are several hypotheses explaining the development of schizophrenia. However, recently the role of oxidative stress and inflammation causing some irreversible alterations in the brain tissue are an explanation to the development of schizophrenia.

Oxidative stress is a condition caused due to imbalance between the excessively produced free radicals and antioxidant system of the body. The brain is vulnerable to the damage caused by oxidative stress indicated by elevated levels of biomarkers of oxidative stress. There are research studies confirming the undoubted effects of antipsychotics treatment on the oxidative stress prevalent in schizophrenic patients.

The interplay of cytokines, interleukins and T-cells in inflammation causes development of elevated levels of free radicals which are potentially toxic to the neurons. Thus increased oxidative stress triggers inflammation whereas redox balance causes inhibition of cellular response. The brain is protected form toxic free radicals by the inherent antioxidant defense mechanism.

The current therapeutic modality suggests the synergistic action of omega -3- fatty acids intake in the diet as well as regular doses of antipsychotics taken in combination as a treatment of Schizophrenia. The omega -3-fatty acids affects and elevates the antioxidant defense mechanisms in schizophrenic patients. This will improve the schizophrenic disease condition, status and further prognosis.

Key Words: Brain, Oxidative stress, Inflammation, Omega -3- fatty acids, Antioxidants

INTRODUCTION

Schizophrenia is a severe mental disorder characterized by disordered thoughts, perceptions, emotions and behavior [1]. World wide prevalence of schizophrenia is 3.8% to 8.4% according to World Health Organization [2].The symptoms of the psychiatric disease can be described as positive symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. lack of motivation, asociality and blunt emotional response) and cognitive deficits[3]. Defective neurotransmitters and altered neurotransmission systems are cited as a cause for schizophrenia [4].

Biomarkers that aid in understanding complex psychiatric disorder like schizophrenia are measured or estimated from post-mortem brain or using in-vivo neuroimaging studies, peripheral biomolecules (e.g. hormones, neurotransmitters or cytokines) and easily available body fluids such as plasma /serum, urine or cerebrospinal fluid [5].

The earliest hypothesis regarding the development of schizophrenia describes disturbances in dopamine metabolism. In addition, recognition that glutamate (N-methyl-D-aspartate-receptors) and gammaaminobutyric acid (GABA) have roles in pathogenesis was cited. Later, the hypothesis that the development of disturbances in some brain areas in schizophrenics supported by neurocognitive impairments in brain due to deterioration in nerve tissue of the brain and gradual progressive disintegration due to alterations in gray matter, occurring in initial period of development during childbirth and adolescence were cited as reasons. Recently, however the role of inflammatory process and oxidative stress causing alterations of brain tissue some of which are irreversible are an explanation to schizophrenia development [6].

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Oxidative Stress and Schizophrenia:

Oxidative Stress is a conditions arising due to excess formation of highly reactive molecules of reactive oxygen species (ROS) and reactive nitrogen species (RNS) resultant of imbalance between the toxic reactive oxygen species and the antioxidant system of the body. This condition leads to tissue damage affecting lipids, proteins and DNA. The antioxidant defense system consists of enzymatic antioxidant system e.g. superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) and non-enzymatic antioxidant systems e.g. vitamins A, C, E, glutathione, uric acid, albumin, bilirubin [1].

Various organs of the human body have different susceptibility to oxidative stress. The brain constitutes 2% of the body weight and utilizes 20% of the oxygen, is the most vulnerable to oxidative damage. The reasons being that brain tissue has increased oxygen utilization, is rich in phospholipids, polyunsaturated fatty acids, transitional metal ions (Cu+ and Fe2+) whereas low in antioxidant levels. [1] [7] The oxidative damage of the phospholipids, DNA and protein contents of the neurons in brain alters their functions such as membrane transport, loss of mitochondrial energy produced, genes expressed, receptors and phospholipids –dependent signal transduction may provide explanation to the altered information processing by the brain in schizophrenia [8].

Several research studies have indicated that the biomarkers of oxidative stress such as Thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA) and 4-hydroxynonenal show increase in activities in the serum of schizophrenic patients in untreated as well as treated patients depicting strong links between oxidative stress and pathophysiology of schizophrenia [7].

Treatment with antipsychotics has an influence on oxidative stress in the course of schizophrenia due to changes in oxidation –reduction balance. Although, there are some studies contradicting this fact the overall undoubted effect of treatment with antipsychotics on the oxidative stress is confirmed in schizophrenia [6].

Inflammatory Response Induces Oxidative Stress in Schizophrenia:

Increased maternal immune system infection may develop the risk of schizophrenia in offsprings. Maternally infected cells may cause increased production of inflammatory cytokines that cross the placenta and result in increase interleukin (IL) 1 β,IL-6,Tumour necrosis factor (TNF-α) and Interferon (IFN –β) etc by fetal cells. Increased cytokines especially interferon-β also cause DNA fragmentation resulting in free radical production. The free radicals cause damage on nuclear and mitochondrial DNA changes in the neurons which is elevated due top high neuronal high energy consumption rate and lack of cell turnover. This leads to progressive development of pathological features and clinical symptoms associated with schizophrenia. Inflammatory responses induced by pro-inflammatory T cells produce free radicals with an ability to modify proteins, lipids and nucleic acids that are potentially toxic for the neurons. Research work indicates T-cell dysfunction, decreased activation of helper T-cells in both treated and untreated schizophrenic patients as compared to healthy controls. Further, detailed genetic studies based on microarray analysis of differentially expressed genes in isolated T-cells from schizophrenic patients and controls which are indicated by transcript changes pertaining to cell cycle machinery, intracellular signaling, metabolism and oxidative stress. This suggests that altered T-cell response may correspond with oxidative stress in some patients suffering from schizophrenia [3].

Oxidative stress and inflammation are related processes. Chronic inflammation is associated with elevated reactive oxygen species levels and anti-inflammatory cascades are associated with reactive oxygen species concentrations in schizophrenia. Increased oxidative stress triggers inflammation whereas redox balance causes inhibition of the cellular response. In degenerative disease like schizophrenia both oxidative stress and inflammation may be cited as etiologic factors leading to pathogenic consequences [9].

Antioxidant Systems in Brain:

Brain is protected from toxicity of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by either

1) removal of ROS/RNS
2) inhibit formation of ROS/RNS
3) binding metal ions needed for catalysis reaction required for ROS/RNS generation.

Glutathione peroxidase (GSH-Px) and glutathione reductase (GR) are well known intracellular antioxidant enzymes. Conversion of peroxides and hydroxyl radicals into non-toxic forms is facilitated by conversion of reduced glutathione (GSH) into oxidized state of glutathione disulfide (GSSG) carried out by glutathione peroxidase. Glutathione reductase recycles GSSG again back to GSH [3] .Superoxide dismutase (SOD) catalyzes the conversion of superoxide radicals to hydrogen peroxide, which is further converted into water by glutathione peroxidase and catalase [7].

Additionally, glutathione –S- transferase and glucose-6-phosphate dehydrogenase detoxifies ROS by decreasing peroxide levels and maintains levels of co-enzymes like glutathione (GSH) and nicotinamide adenine dinucleotide phosphate necessary for primary antioxidant enzymes. Similarly, thioredoxin and thioredoxin reductase maintains the level of antioxidant molecules for e.g. ubiquinone, lipoic acid, ascorbic acid (vitamin C) capable of counteracting ROS/RNS. Other antioxidant defense mechanisms include α-tocopherol (Vitamin E), bilirubin, albumin, uric acid, niacin, carotenoids and flavonoids [3].

In the case of the antioxidants of schizophrenic patients contrasting research studies results are obtained due to differences in species e.g. rats and humans , different tissues e.g. brain and serum, therapeutic features and duration of the disease. In schizophrenic patients it should be noted that there are differences between untreated and treated also the oxidative stress status of patients should be taken into consideration and whether treated with anti-psychotics typical or atypical in nature [7].

Current Therapeutic Modalities

The dietary intake of essential polyunsaturated fatty acids is suggested considering the dysfunction of membrane phospholipids metabolism in all the cells of the body from the onset of psychosis in patients with schizophrenia .Reduced levels of membrane essential polyunsaturated fatty acids e.g. arachidonic acid, eicosapentanoic acid, docosapentaenoic acid or docosahexaenoic acid and their role in psychopathology of schizophrenia have been reported in treated and untreated patients even after the first episode of psychosis. The membrane phospholipids have an important role in membrane receptor-mediated signal transduction of several neuro-transmitters and growth factors contributing to abnormal information processing in schizophrenia. A combination of eicosapentanoic /docosahexaenoic acid or omega -3- polyunsaturated fatty acids and antioxidant vitamins like C and E causes significant reduction of psychopathology of schizophrenia. This is an indication that essential polyunsaturated fatty acids supplementation could be an effective treatment to cause improvement for the outcome of the disease over an extended period of time [7].

Therapy of utilizing antioxidants have the potential to delay or decrease many psychiatric disorders like schizophrenia. Treatment with N-acetylcysteine (NAC) a rate limiting factor in the synthesis of glutathione (GSH) has been reported to improve the core symptoms of Schizophrenia. The NAC treatment increased glutathione (GSH) levels restoring its levels and improving N-methyl-D-aspartate receptor function implicated by auditory response of brain in research studies [3].

Fish oil (long –chain omega -3- polyunsaturated fatty acids –PUFA's) is a commonly used supplement in the general population with the aim of preventing oxidative stress. Recent study reported that supplementation with fish oil significantly reduced the progression to first episode psychosis (FEP) in schizophrenic patients. This study proves that oxidative stress may prove to be a biomarker of schizophrenia risk and therefore has response to antioxidant treatment [10].Omega -3- fatty acids elevates the antioxidant enzymes and reduces oxidative stress in the brain and possesses synergistic action with anti-psychotic medicine and improved schizophrenic symptoms. This synergistic action of antioxidants certainly plays a therapeutic role and suggests a possible new schizophrenic treatment strategy [1]. This also emphasizes the possible importance of dietary nutrient antioxidant supplementation to enhance the antioxidant defense system in body in schizophrenic patients [7].

CONCLUSION

Oxidative stress appears to be the key component in schizophrenic patho-physiology. The oxidative stress contributes to be a central point among the other factors which interact to cause the psychiatric disease schizophrenia. The combination of supplements of antioxidant treatment as well as dosages of regular treatment of antipsychotics will support the endogenous antioxidant system and will synergistically improve the schizophrenic disease condition, status and further prognosis.

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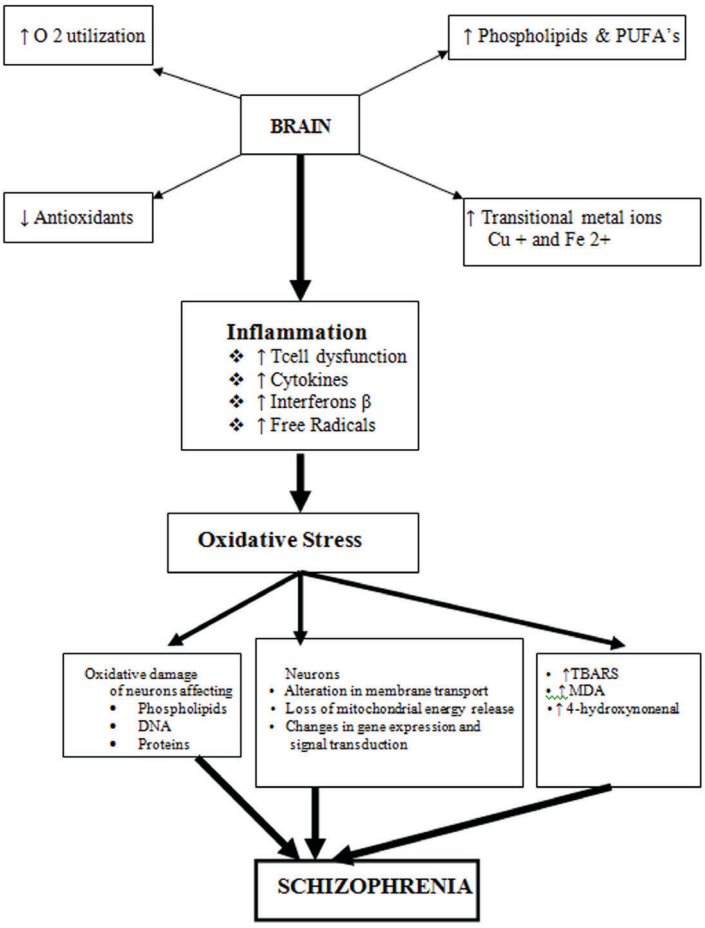

Figure 1: Role of Oxidative Stress and Inflammation in Schizophrenia.

Table 1: Antioxidant System of Brain

Enzymatic Antioxidants	Non Enzymatic Antioxidants
⇨ Glutathione peroxidase (GPx)	■ Vitamin C (Ascorbic acid)
⇨ Glutathione reductase (GR)	■ VitaminE (α -tocopherol)
⇨ Superoxide dismutase(SOD)	■ Bilirubin
⇨ Catalase (CAT)	■ Albumin
	■ Uric acid
	■ Niacin
	■ Carotenoids
	■ Flavonoids
	■ Lipoic acid
	■ Thioredoxin